REMARKS

Applicant's representative thanks the examiner for the courtesies extended to Applicants' representatives during the telephone interview on September 13, 2002.

In the final Office Action dated March 12, 2002, the examiner found claims 23-26, 29 and 30 are free of prior art while maintaining the rejection of claims 1-22, 27, 28 and 31-53. In the response filed in June 12, 2002, without acquiescing the examiner's position in the rejections, applicant cancelled the rejected claims 1-22, 27, 28 and 31-53 to advance the case towards allowance. At the same time, because claims 23-26 were dependent from the cancelled claim 1, applicant has rewritten claims 23-26 to be independent claims by removing the reference to claim 1. That is, claims 23-26 were amended to recite the actual claim languages of claim 1, instead of being dependent from claim 1. Thus, the only change in claims 23 –26 made in the amendment of June 12, 2002 is the change of claim form from a dependent claim to an independent claim.

However, the Advisory Action mailed September 6, 2002, has denied the entry of the amendment alleging that "(1) the incorporation of claim 1 into claims 23-26 has changed the scope of these claims, and as such has moved claims 23-26 from allowable status to rejected status; and (2) applicant's amendment would also raise new issues that would require additional searching."

As explained above and also during the telephone interview, however, the only change applicant contemplated by this amendment is to rewrite claims 23-26 as a independent claims as a result of the cancellation of claim 1 from which claims 23-26 were originally dependent. Therefore, applicant respectfully submits that such an amendment of claims 23-26 does not change the scope of these claims that are originally determined to be free of prior art. As a result, the amendment of claims 23-26 does not raise new issues the examiner needs to conduct a new search.

Accordingly, applicants respectfully request entry of the foregoing amendments that are identical to those filed June 12, 2002, which should place the case in condition for allowance. Thus, an early notice to this effect is earnestly solicited.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date Oct. 15, 2002 By Stephen B. Maebius

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

23. (Amended) A [The] method [of claim 1, wherein the targeting protein comprises] for targeting a therapeutic agent to a target site in a patient, comprising the steps of:

(a) administering to the patient an effective amount for targeting of at least one multispecific targeting protein comprising at least two first binding sites which specifically bind to the same or different epitopes of the same or different substance produced by or associated with the target site and present at the target site, and at least one second binding site which specifically binds to an epitope of at least one enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, administering to the patient an amount effective for clearance of a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) administering to the patient an effective amount for enzyme activity of the enzyme, such that the targeting protein binds the enzyme to form a non-covalent targeting protein-enzyme conjugate in situ;

(d) optionally, administering to the patient an amount effective for clearance of a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation;

(e) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme administered in step (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out the target site that it accretes at the target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.

24. (Amended) A [The] method [of claim 1, wherein step (a) comprises administering] for targeting a therapeutic agent to a target site in a patient, comprising the steps of:

(a) administering to the patient an effective amount for targeting of at least two different multispecific targeting proteins each of which [comprise] comprises a first binding site which specifically binds to an epitope of a different substance produced by or associated with the target site and present at the target site, and each of which comprises at least one second binding site which specifically binds to an epitope of at least one enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, administering to the patient an amount effective for clearance of a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) administering to the patient an effective amount for enzyme activity of the enzyme, such that the targeting protein binds the enzyme to form a non-covalent targeting protein-enzyme conjugate in situ;

(d) optionally, administering to the patient an amount effective for clearance of a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation;

(e) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme administered in step (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out the target site that it accretes at the target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.

25. (Amended) A [The] method [of claim 1, wherein the targeting protein comprises] for targeting a therapeutic agent to a target site in a patient, comprising the steps of:

(a) administering to the patient an effective amount for targeting of at least one multispecific targeting protein comprising at least one first binding site which specifically binds to at least one epitope of at least one substance produced by or associated with the target site and present at the target site, and at least two second binding sites which specifically bind to different enzymes, [and wherein step (c)

comprises administering the different enzymes] wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, administering to the patient an amount effective for clearance of a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) administering to the patient an effective amount for enzyme activity of the different enzymes, such that the targeting protein binds the enzymes to form a non-covalent targeting protein-enzyme conjugate in situ;

(d) optionally, administering to the patient an amount effective for clearance of a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation;

(e) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme administered in step (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out the target site that it accretes at the target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.

26. (Amended) A [The] method [of claim 1, wherein step (a) comprises administering] for targeting a therapeutic agent to a target site in a patient, comprising the steps of:

(a) administering to the patient an effective amount for targeting of at least two different multispecific targeting proteins each of which comprises at least one first binding site which specifically binds to at least one epitope of at least one substance produced by or associated with the target site and present at the target site, and each of which [comprise] comprises a second binding site which specifically binds to an epitope of a different enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, administering to the patient an amount effective for clearance of a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) administering to the patient an effective amount for enzyme activity of the different enzymes, such that the targeting protein binds the enzymes to form a non-covalent targeting protein-enzyme conjugate in situ;

(d) optionally, administering to the patient an amount effective for clearance of a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation;

(e) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme administered in step (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out the target site that it accretes at the target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.